REMARKS

Upon entry of the foregoing amendments, allowed claims 33, 34 and 49-52, and currently rejected claims 53-58 will be pending in the application. Claims 33, 53 and 56 are independent claims.

There are no outstanding prior art rejections.

Independent claims 53 and 56 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The amended claims now recite that the amino acid sequence comprises the entire conserved region amino acids of SEQ ID NO:23 or SEQ ID NO:35, respectively, and that the isolated protein of each claim is not a wild type NhhA polypeptide. These claims have also been amended to correct the spelling of the microorganism *N. meningitidis*.

Support for the amendment reciting "*and which comprises the entire conserved region amino acids of SEQ ID NO:23 or SEQ ID NO:35, respectively,*" is generally supported by the specification as originally filed, although particular reference is made to page 2, lines 30-31, and page 11, lines 11-16, for example.

Support for the amendment reciting "*is not a* wild *type NhhA polypeptide*" can be found at page 3, lines 1-6, as originally filed, for example.

Since no new matter has been added by the amendments, their entry is respectfully solicited.

Applicants traverse the rejections of claims 53-58 under the first and second paragraphs of 35 USC §112 for the following reasons.

35 USC §112 - Enablement

The Examiner has rejected former claims 53-58 as lacking enablement.

The Examiner's rejection may be summarized as follows:

1. The specification does not shown how to make variants of SEQ ID NOS:23 or 35 that possess the recited function of eliciting an immune response to a plurality of strains of *N. meningitidis*.

2. Neither FIG. 1 or Table 1 of the specification explains which amino acids of SEQ ID NOS:23 or 35 should be modified within the constraints of 80% or 90% amino acid sequence identity.
3. The specification is silent as to which specific immunoepitopes, fragments or variants confer immune responses to a plurality of strains of *N. meningitidis*.
4. Protein chemistry is an unpredictable area, particularly with respect to defining and designing epitopes that will elicit an immune response to a pathogen.

In response, claims 53 and 56 have been amended to recite that within the limit of 80% or 90% sequence identity, the claimed variant comprises the entire conserved region amino acids of SEQ ID NO:23 or SEQ ID NO:35, respectively.

The enablement rejection will be addressed only in so far as the Examiner may consider the rejection relevant to amended claims 53 and 56.

Effectively, in claims 53 and 56, the only amino acid sequence variation is in regions other than the conserved regions present in SEQ ID NOS:23 or 35. In other words, the relatively low level of variation is restricted to the V region amino acids in SEQ ID NOS:23 or 35. This addresses the Examiner's concern that no guidance is provided by the specification that explains which amino acids can be changed and which must be retained to confer immune responses to a plurality of strains of *N. meningitidis*.

The specification has always disclosed that it is preferred to retain conserved regions, as these confer immune responses to a plurality of strains of *N. meningitides*. Thus, these regions are called "conserved" regions. Accordingly, the specification does provide guidance with respect to the portions of SEQ ID NOS:23 or 35 that confer immune responses to a plurality of strains of *N. meningitidis*. Consistent with this, claims 53 and 56 recite that these conserved amino acids must be retained. The accompanying V regions (V3 and V4; with a few V1 amino acids in SEQ ID NO:23) constitute only about 40 amino acids of each of SEQ ID NOS: 23 and 35.

20% variation in these V regions, corresponding to the 80% identity claimed in claim 53, amounts to only about 8 amino acid changes.

10% variation in these V regions, corresponding to the 90% identity claimed in claim 56, amounts to only about 4 amino acid changes.

By way of example only, referring to Figure 1 it can be seen that in V3 of SEQ ID NO:1 (strain PMC21; from which SEQ ID NOS:23 and 35 were created), variation at residue 201 could be L → A, residue 202 N → G, residue 203 T → S, residue 204 G → S and so forth, based purely on the natural variation that occurs at corresponding residues in other *N. meningitidis* strains disclosed in Figure 1. It would not be difficult for a person of ordinary skill in the biotechnology art to make these variants which retain all conserved region residues (which are responsible for broad spectrum immune responses); nor would it be difficult to use these as immunogens. This does not constitute undue experimentation.

With respect, Applicants submit that the Examiner's comments on the unpredictability of protein chemistry and the Examiner's comments that predicting the immunogenicity of proteins is purely an empirical science that requires undue experimentation are not well-founded or warranted.

More specifically, there are several predictive methods of defining the immunogenicity of a protein without having to resort to the kind of empirical, undue experimentation referred to by the Examiner:

One method of predicting protein immunogenicity is bioinformatic analysis. Immunogenicity can be predicted by analysis of the probability that a particular region of a protein is exposed on the surface of the protein. This prediction is based on a number of physical characteristics of the protein sequence including hydrophobicity (Hopp, T.P. and Woods, K.R., 1983, A computer program for predicting protein antigenic determinants. *Mol. Immunol.* 20, 483–489); the relative occurrence of amino acids in antigenic regions (Welling, G.W., Weijer, W.J., van der Zee, R., and Welling-Wester, S., 1985, Prediction of sequential antigenic regions in proteins. FEBS Lett, 188(2):215-218); and surface accessibility and flexibility (Kolaskar, A. S. and Tongaonkar, P.C., 1990, A semi-empirical method for prediction of antigenic determinants on protein antigens. FEBS Lett, 276(1-2):172-174). Software is readily available that allows these "antigenicity analysis" predictions to be performed. Use of this software would allow determination of which 80% or 90% variants of proteins according to SEQ ID NOS:23 or 35 are more likely to be antigenic and thereby represent variants that will confer immune responses to a plurality of strains of *N. meningitidis*.

Copies of each of these documents are being submitted with a Supplemental Information Disclosure Statement being filed contemporaneously today with this Amendment.

Reconsideration and withdrawal of the asserted lack of enablement rejection are respectfully solicited.

35 USC §112 - New Matter

The allegedly offending recitation reciting "*is not a* full *length NhhA polypeptide*" has been replaced in the claims by reciting "*is not a wild type NhhA polypeptide,*" which is fully supported by the application as filed. Accordingly, reconsideration and withdrawal of the asserted new matter rejection are respectfully solicited.

35 USC §112 - Written Description

Because the allegedly offending recitation "*is not a full length NhhA polypeptide*" has been replaced in the claims by the recitation "*is not a* wild *type NhhA polypeptide,*" which is fully supported by the application as filed. Accordingly, reconsideration and withdrawal of the rejection based on the asserted lack of a sufficient written description rejection are respectfully solicited.

35 USC §112 - Indefiniteness

The allegedly offending recitation reciting "*is not a full length NhhA polypeptide*" has been replaced in the claims by reciting "*is not a wild type NhhA polypeptide,*" which is fully supported by the application as filed. Accordingly, reconsideration and withdrawal of the rejection based the asserted indefiniteness rejection are respectfully solicited.

While Applicants appreciate the prior indication of allowability of claims 33, 34 and 49-52, and the withdrawal of the previous prior art rejections, reconsideration and withdrawal of all of the rejections of claims 53-58 and an early Notice of Allowance relating to all claims are respectfully solicited.

Also submitted contemporaneously today with this Amendment and with the above-mentioned Information Disclosure Statement is a document entitled Notification Of Loss Of Entitlement To Small Entity Status Under 37 C.F.R. § 1.27(G)(2) And Request For Excused

Erroneous Payment Of Prior Fees As Small Entity Under 37 C.F.R. § 1.28(c), since the undersigned attorney was recently informed of a license of rights in this application to a large entity. All prior fees paid during the prosecution of this application were paid by error without deceptive intention on the basis that Applicants and their assignee were small entities. This document authorizes the payment of all prior fees as itemized therein to be paid as large entity fees.

Applicants respectfully submit that this application is now in complete condition for allowance.

Respectfully submitted,

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(Date)

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